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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/597,767 | 08/07/2006 | J. David Schaffer | PHUS040120US3 | 3848 |

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| EXAMINER | |
|---|---|
| WHALEY, PABLO S | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1631 | |

| NOTIFICATION DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| *Office Action Summary* | Application No. | Applicant(s) |
|---|---|---|
| | 10/597,767 | SCHAFFER ET AL. |
| | Examiner | Art Unit |
| | PABLO WHALEY | 1631 |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-24 and 26* is/are pending in the application.

4a) Of the above claim(s) *3, 4, 7, 8, 22, and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,9-21,24 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____

## DETAILED ACTION

Applicant's arguments, filed 12/21/2010, have been fully considered.

Applicant's repeated arguments that Species i, ii, iii, and iv, as set forth in the Office action mailed 08/17/2010, are not mutually exclusive have been fully considered but are not persuasive for at least the following reasons. Namely, generating offspring chromosomes based on values within a range is divergent from methods that generate offspring based on filling genes with common values, and replacement based on fitness. Accordingly, claims 3, 4, 7, 8, 22, and 23 remain withdrawn from consideration.

The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicants have amended their claims, filed 12/21/2010, and therefore rejections newly made in the instant office action have been necessitated by amendment.

### *Status of Claims*

Claims 1-24 and 26 are pending. Applicant has cancelled claim 25.

Claims 1, 2, 5, 6, 9-21, 24, and 26 are under consideration.

### *Objections*

The objection of claims 12 and 13 for grammatical errors with withdrawn in view of applicant's amendments to the claims.

### *Claim Rejections - 35 USC § 101*

**Response to Arguments**

Applicant's arguments, filed 12/21/2010, that the claimed methods are statutory

in view of the amendments are persuasive. Therefore the rejection is withdrawn.

### ***Claim Rejections - 35 USC § 103***

**Response to Arguments**

Applicant's arguments, filed 12/21/2010, have been fully considered but are not persuasive for the following reasons.

In response to applicant's arguments that Ooi and Chtioui do not teach expressed sub-set-size genes wherein each gene contains an index value indexing a measurement, Ooi teaches chromosomes associated with an ordered set of genes; see page 39, Col. 1, ¶4, and Fig. 2, which read on sub-set-size genes since they occur in sets. Furthermore, Ooi does not specifically teach genes containing index values which index a measurement of the associated sets of measurements, as in claims 1, 15, 19, and 21. However, Ooi suggests this limitation because the genes used in the process taught by Ooi are indexed; see, e.g. page 38, col. 2, ¶2, and page 39, col. 1, ¶5, and these index values are associated with frequency measurements and are used in expression profiles; see Figures 1 and 2. Therefore, Ooi makes obvious the use of genes with index values for indexing measurements.

In response to applicant's arguments that Ooi does not teach adding an additional gene specifying R and evolving that added gene to optimize the number of features used in the classification, the claims do not recite these limitations. The claims do not recite any limitations related to the number of genes that can or cannot be evolved. The claims require generating offspring chromsomes, but that does not appear

to be the same as adding a gene.

In response to applicant's argument that Ooi and Chtioui do not teach expressed sub-set-size genes having a value distinguishing expressed and unexpressed genes, Ooi was not relied upon as a teaching for this limitation. Chtioui exemplifies binary chromosomes used in evolving populations; e.g. see page 79, Col. 2, where the 0 and 1 values shows expressed and unexpressed genes in a sequence, which reads on values distinguishing expressed and unexpressed genes.

In response to applicant's arguments that Chtioui does not teach sub-set-size genes wherein each gene contains an index value indexing a measurement, Ooi was relied upon for this teaching, as set forth above.

In response to applicant's arguments that the binary genes taught by Chtioui comprising binary selection values would adversely affect scalability [Remarks, page 13], the claims at issue are not directed to a method for determining scalability and the response has not provided any evidence that the art, when combined, would have resulted in an inoperative invention.

In response to applicant's arguments that Chtioui does not teach ordinary position values, the binary values taught by Chtioui used for crossover in evolving populations provide information related to the presence/absence of genes in a sequence and thus inherently provide ordinal information; e.g. see page 79, Col. 2.

In response to applicant's arguments that Ooi and Chtioui do not teach mutation rates greater than 5% since this value is 250 times larger than the rate taught by Ooi, mutation rate is a design parameter of genetic algorithms, and Ooi teaches methods for

predictably calculating mutation rates of genes up to 0.02%. Therefore, one skilled in the art would have been motivated to improve genetic algorithm performance based on variations of known design incentives, such as using higher mutation rates, since these variations are predictable to one of ordinary skill in the art.

In response to applicant's argument regarding limitations directed to noise, Ooi and Chtioui do not teach introducing a selected level of noise into values of measurements of the measured subjects, as in claims 11, 19, and 26. However, Liu describes the addition of noise into measurement data at a number of different points; see page 297, Col. 2, as set forth below.

For these reasons, the examiner maintains that the combination of references teaches and/or makes obvious the claimed limitations. However, the rejection has been modified to address applicant's amendments.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 5, 6, 9, 10, 13, 14, 15, 17, 18, 19, 20, 21, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ooi et al. (Bioinformatics, 2003, Vol. 19, No. 1, p.37-44), in view of Chtioui et al. (J. Sci. Food Agric., 1998; IDS filed 08/07/2006).

Claims 1, 15, 19, and 21 are directed to a method for determining a classifier by producing a first generation chromosome population of chromosomes. Each chromosome has a selected number of genes specifying a sub-set of associated measurements; which are interpreted as spots on a microarray (in light of the Specification on page 3). Index values are used for indexing measurements of the genes. Each chromosome also has an expressed sub-set-size gene having a value distinguishing expressed and unexpressed genes; which are interpreted as an expression level or a binary value corresponding to genes on a microarray (in light of the Specification on pages 3, 10, and 11). The claims also require genetically evolving

genes of the chromosomes to a fitness criterion evaluated without reference to unexpressed genes, to produce successive generation populations. The claims result in selecting a classifier that uses the sub-set of associated measurements specified by the expressed genes. Claims 13, 18, and 20 are directed to medical diagnostic tests for determining whether a subject has a pathology by classifying measurements of the medical subject using diagnostic classifiers.

Ooi teaches genetic algorithms applied to the analysis of gene expression data. The genetic algorithm (GA) is based on the selection of the best individuals for reproduction. In particular, the process requires producing a chromosome string wherein each chromosome is associated with an ordered set of genes and a particular parameter (i.e. set of measurements); see page 39, Col. 1, ¶4, and Fig. 2. Therefore, the genes taught by Ooi are interpreted as sub-set-size genes since they occur in sets, and since the specification does not provide a limiting definition for “sub-set-size genes”.

Regarding limitations directed to index values, Ooi does not specifically teach genes containing index values which index a measurement of the associated sets of measurements, as in claims 1, 15, 19, and 21. However, Ooi suggests this limitation because the genes used in the process taught by Ooi are indexed; see, e.g. page 38, col. 2, ¶2, and page 39, col. 1, ¶5, and these index values are associated with frequency measurements and are used in expression profiles; see Figures 1 and 2. Therefore, Ooi makes obvious the use of genes with index values for indexing measurements.

The process of genetically evolving chromosomes is described; see page 39, Col. 1, wherein genes are selected for mating based on a fitness criterion. These genes undergo mating by applying genetic operators to produce successive chromosome populations; see page 39, Col. 1 and Col. 2. This process is repeated until a predictor set of genes with the best fitness is obtained; see at least pages 39, Col. 2 and Fig. 2, which shows selecting a classifier based on a sub-set of associated fitness measurements and replacement of genes with improved fitness. Ooi also shows this entire process applied to gene expression data. In particular, microarray gene expression data sets are disclosed; see page 38, Col. 2. Several different values are described that can be used to distinguish the expressed genes; e.g. intensity ratio values and index values; see page 38, Col. 2. Empty spots (i.e. unexpressed genes) on the microarray are excluded from the genetic evolution process; see page 38, Col. 2, which shows evaluation without reference to unexpressed genes.

Regarding claims 13, 18, and 20, Ooi also describes a classifier selection procedure using gene expression data obtained from tumor samples; page 39-40, MLHD Classifier section, wherein Cy5/Cy3 ratios correlate to concentrations of fluorescent markers. The genetic algorithm of Ooi is also applied to a cancer study. More specifically, a data set comprising 14 classes of tumors is classified using the GA; see page 43, Col. 1, which shows using a medical diagnostic classifier for classification into positive and negative groups, since the results are associated with an error rate (i.e. 18% error), which implies 82% positive classification). Ooi discloses mutation rates of genes as high as 0.02%; see Table 1.

Ooi does not teach an expressed gene having a value distinguishing expressed and unexpressed genes of the chromosome, as in claims 1, 15, and 19.

Ooi does not teach an expressed gene containing an ordinal position value, as in claim 2.

Ooi does not teach filling genes of the offspring with gene values common to both parent chromosomes, as in claim 5, or occasionally varying the ordering of the common gene values in offspring, as in claim 6.

Ooi does not teach a mutation rate for the selective mutating of the gene value that are unique to one or the other of the parent chromosomes that is greater than 5%, as in claim 16.

Chtioui teaches methods of feature selection based on genetic algorithms. In particular, pages 79 discuss the genetic algorithm in detail and describes steps for producing a first generation chromosome population (#1, #2), genetically evolving the population respective to a fitness criterion (#3 through #7), and selecting a parameter (i.e. classifier)(#1). Chtioui exemplifies binary chromosomes with values 0 and 1 used for crossover in evolving populations; e.g. see page 79, Col. 2, which meets claim language for genes having an ordinal position value distinguishing expressed and unexpressed genes of the chromosome, as the binary values inherently provide ordinal information regarding the presence/absence of genes in a sequence. Each child receives one segment of bits from each parent; see page 79, Col. 2, which shows filling offspring with gene values common to both parent chromosomes. Crossover and

mutations are performed; see page 79, col. 2, which shows randomly altering values of each chromosome.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have used values distinguishing expressed and unexpressed genes of the chromosome, as taught by Chtioui, in the method of Ooi, since Ooi also teaches crossover and suggests the use of binary classification methods; see page 40, Col. 2, ¶4. The motivation would have been to compare classifier performance by comparing predictor gene sets discovered by different methods, as suggested by Ooi; see page 40, Col. 2, ¶4.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have modified the method of Ooi by using ordinal position values, filling genes of the offspring with gene values common to both parent chromosomes, and occasionally varying the ordering of the common gene values in offspring, as taught by Chtioui, with a reasonable expectation of success, since Ooi also teaches a genetic evolving process based on crossover and mutation of genes with predictable results. The motivation would have been to avoid premature convergence to improve population diversity, as suggested by Chtioui; see page 79, Col. 2.

It would have been obvious for one of ordinary skill in the art at the time of the instant invention to have provided a predictable variation of the step for selectively mutating genes, such as limiting it to provide a mutation rate that is greater than 5%, with a reasonable expectation of success, in view of the prior art of Ooi, who shows that mutation rate is a design parameter of genetic algorithms, and predictably calculates

mutation rates of genes up to 0.02%; see page 39, Col. 2, page 41, Col. 1, and Table 1, and in view of the rationale for a *prima facie* case of obviousness provided by the Supreme Court in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1395-97 (2007). See also MPEP 2143. In this case, the rationale would have been to explore methods for improving genetic algorithm performance based on variations of known design incentives, such as using higher mutation rates, since these variations are predictable to one of ordinary skill in the art. For these reasons, the instant claims do not recite any new element or new function or unpredictable result.

Claims 11, 12, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ooi et al. (Bioinformatics, 2003, Vol. 19, No. 1, p.37-44), in view of Chtioui et al. (J. Sci. Food Agric., 1998; IDS filed 08/07/2006), as applied to claims 1, 2, 5, 6, 9, 10, 13, 14, 15, 17, 18, 19, 20, 21, 24, and 25, above, and further in view of Liu et al. (Evolutionary Computation, 2002, 12-17 May 2002, pages: 297 – 302).

Ooi and Chtioui make obvious a method for determining a classifier, as set forth above.

Ooi and Chtioui do not teach introducing a selected level of noise into values of measurements of the measured subjects, as in claims 11, 19, and 26.

Ooi and Chtioui do not teach randomly or pseudo randomly splitting a set of measured subjects into training groups and test groups before producing successive

generation chromosome populations, as in claim 12. It is noted that splitting a set of measured subjects into training groups and test groups before producing successive generations is interpreted as step of cross-validation, in light of the specification; see page 18.

Liu teaches a method for selecting informative genes using an evolutionary algorithm. In particular, Liu describes the addition of noise into measurement data at a number of different points; see page 297, Col. 2. Liu also describes a validation process wherein training data is randomly shuffled into two subsets, one for constructing a classifier and one for evaluating the classifier; see page 298, col. 2.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have introduced noise into values of measurement data, as taught by Lui, prior to any of the successive generation steps taught in the method made obvious by Ooi and Chtioui, since Ooi already shows the presence of noise in gene expression data; see page 41, col. 1. The motivation would have been to test the performance of simple standard deviation filters to improve fitness, for example, as suggested by Ooi on page 41, Col. 1.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have randomly split a set of measured subjects into training groups and test groups before producing successive generation chromosome populations, in the method made obvious by Ooi and Chtioui, in view of Liu, who teaches a validation process wherein training data is randomly shuffled into two subsets, one for constructing a classifier and one for evaluating the classifier; see page 298, col. 2.

Additionally, Ooi teaches cross-validation prior to each evolutionary step, and suggests other cross-over strategies with predictable results; see page 41, col. 1. In each case, the motivation would have been to apply known cross-validation techniques to obtain an optimal set of classifiers, as suggested by Liu; see page 298, col. 2.

## ***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached between 11am-7pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**Pablo S. Whaley**

Patent Examiner

Art Unit 1631

/PW/

/Marjorie Moran/
Supervisory Patent Examiner, Art Unit 1631